

# THE TRANSFER OF RADIOIODINE ACROSS PLACENTA AND BREAST

JOHN GERSTEN

*Department of Anatomy, The Ohio State University, Columbus 10*

It is common knowledge that both the fetus and the nursing young receive their nourishment from the mother; the one by way of the placenta, and the other by way of the breast. Part I of this investigation, deals with the passage of iodine from mother to fetus and is largely in the nature of a review, while Part II, which pertains to the passage of iodine back and forth across the placenta is, to my knowledge, original work.

The first experimental evidence for the transfer of known substances across the placental barrier from mother to fetus was published by Mayer (1817) who gave indigo and safranin to the pregnant rabbit. Subsequently a great deal of investigative work has been done, and Nicoloux (1909) presented in his excellent review the most important researches in this field prior to 1909.

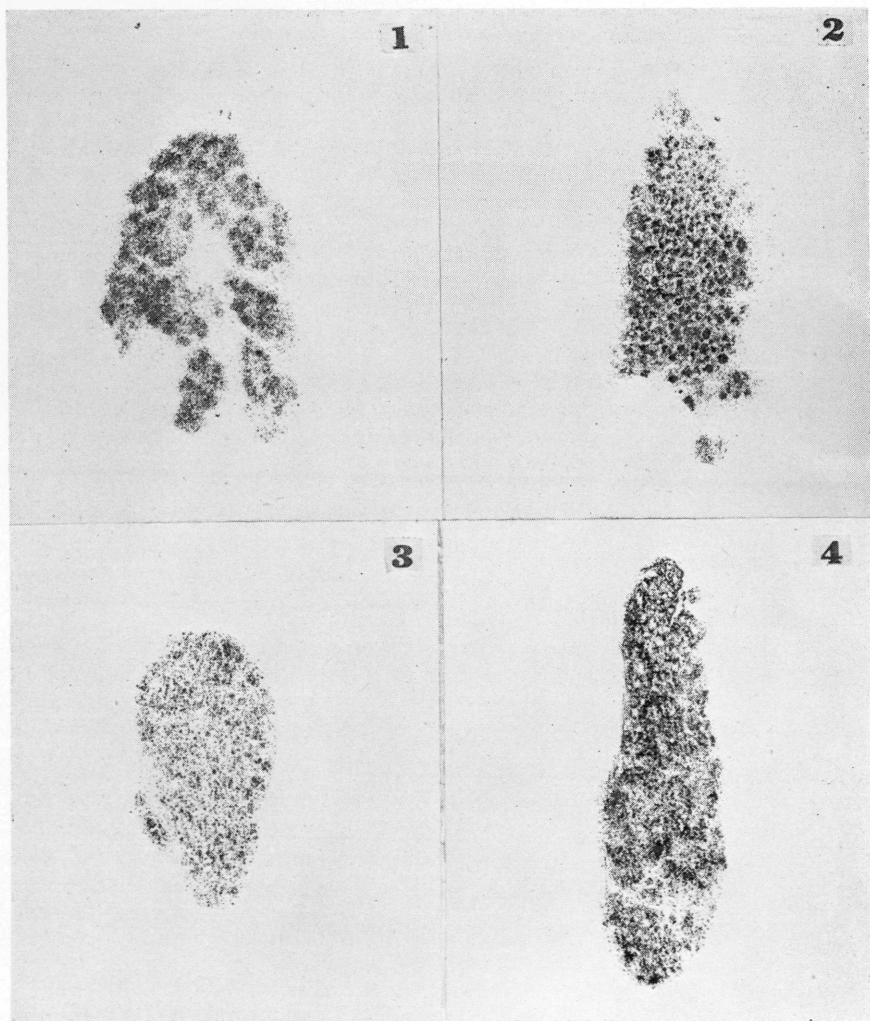
Schaunenstein and Spaeth (1859) demonstrated a strong iodine reaction in the amniotic fluid of rabbits after potassium iodide has been added to the mother's diet. Gusserow (1872) obtained similar findings in man. A few years later, Krukenberg (1885) after an extensive series of investigations confirmed this previous work and postulated that the permeability of the placenta varied with the duration of the gestation period, and that the closer to term the more readily was iodine transferred across the placental membrane. This concurs with Mossman's work (1925) and furthermore demonstrates that, near the end of gestation in the rabbit, only the fetal endothelium forms the principal barrier between fetal and maternal blood streams.

The beginning of the twentieth century brought a developing awareness of the therapeutic value of iodine. Thus, it was found that supplementary dietary iodine in pregnant sheep markedly reduced the high fetal mortality due to "fetal athyreosis." Similar results were obtained with newborn calves and colts. Following the same trend, Smith (1917) prevented fetal myxedema in pigs by adding one gram of potassium iodide daily to the mother's diet. The remarkable reduction of the incidence of cretinism in the Swiss canton of Appenzell by simply giving the pregnant mother adequate supplementary iodine climaxed this period of empiric therapeutic treatment (Curtis and Fertman, 1943).

Actual quantitative increases in the iodine content of the fetal thyroid gland following additional dietary iodine for the mother were obtained by Hudson (1931) who used finer analytical methods than had been previously available. To Hertz, Roberts, and Means (1938) should go much of the credit for pioneer work using radioactive iodine as a new tool in the investigation of thyroid physiology. The first good auto-radiographs of the human thyroid gland in both normal and abnormal states were those of Hamilton, produced in 1942. Using the same technique, Gorbman and Evans (1943), showed that the fetal rat does not significantly accumulate maternally injected radioiodine until the eighteenth or nineteenth day of its twenty-one day gestation period. This fetal stage corresponds to the time of appearance of definitive thyroid follicles and the accumulation of colloid within them.

The transfer of known chemical substances from mother to *nursing* offspring has also been the subject of extensive study. Obstetricians have long been aware of the effect upon the nursing child of the maternal intake of such drugs as alcohol, morphine, cathartics, ether, etc. (DeLee and Greenhill, 1947). In 1908 Reijst-

Scheffer showed that the feeding of potassium iodide to cows increased the iodine content of the whey; and Scharrer (1927) showed that adding the same substance to the diet of the lactating goat could result in a twenty-fold increase in the iodine content of its milk within thirty minutes. In the human infant, under normal

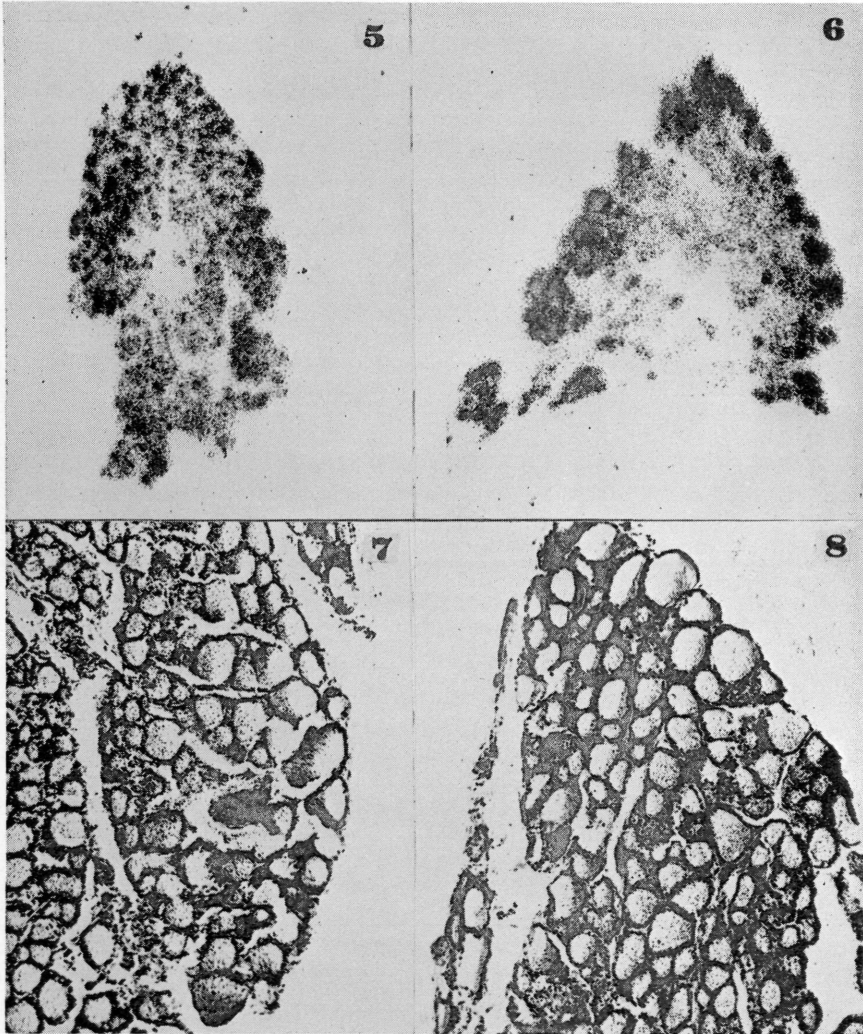


FIGURES 1-4. Auto-radiographs of thyroids of pre-nursing rats.  
FIG. 4. Thyroid of still-born rat.

conditions, the intake of iodine by way of breast milk becomes relatively high beginning on the sixth day post-partum, (Elmer and Rychlik, 1934). Using relatively high doses of radioactive iodine, Rugh (1950, 1951) found that in mice the lactating mammary glands serve as excretory channels for the elimination of extra iodine intake, and that nursing mice have a high uptake of the iodine in their thyroid glands.

Much less voluminous are the investigations relating to the passage of substances across the placenta from *fetus* to mother. Snyder (1943) has found that intrafetal

injections of certain hormones, among which are pituitrin, anterior pituitary extract, and parathyroid extract fail to reach the maternal circulation or to have any effect on the maternal economy, whereas phenolsulphonephthalein was transferred readily across the placental barrier.



FIGURES 5-8. Auto-radiographs of thyroids of several nursing rats.

#### MATERIALS AND METHODS

*Part 1.* Two groups of six rats each were used. All individuals of Group I were pregnant rats near term. Group II rats were in a post-partum lactating condition. Each adult animal was kept in its own individual cage and each received a single subcutaneous injection of radioactive, carrier-free iodine of eight day half-life ( $I^{131}$ ).<sup>1</sup> The dose of radioiodine given was calculated on the basis of one micro-

<sup>1</sup>Radioactive iodine was furnished through the Atomic Energy Commission, Oak Ridge, Tenn., and Dr. Wm. Myers, Dept. of Physiology, The Ohio State University, Columbus, Ohio.

curie for every ten grams of body weight. This amount is comparable to the therapeutic doses being given to human beings.

Group I (pregnant) rats received the  $I^{131}$  from one to three days prior to the estimated day of parturition. The newborn of this group were all sacrificed before their first nursing attempt. These newborn animals are therefore designated as pre-nursing offspring.

Group II (lactating) rats received the injection of  $I^{131}$  a variable time after delivery—from within a few hours to several days. The young were sacrificed after having nursed one or more times. These new-born animals are therefore designated as *nursing offspring*.

Stained and unstained histological sections were prepared of the thyroid glands of all the sacrificed animals of both groups. Autoradiographs of these sections were prepared after the technic of Bélanger and Leblond (1946), and their associates, (Leblond, Percival and Gross, 1948). This method consists essentially of coating the sections with a sensitive photographic emulsion, followed by a suitable exposure time. The slides are then developed. The deposition of tiny black granules (silver) upon the histological sections indicates the approximate location of the disintegrating radioactive particles in the tissues. Owing to varied exposure time intervals elapsing before developing the different slides, the intensity of granular blackening must not be construed as representing a quantitative index of the uptake of radioiodine in these sections.

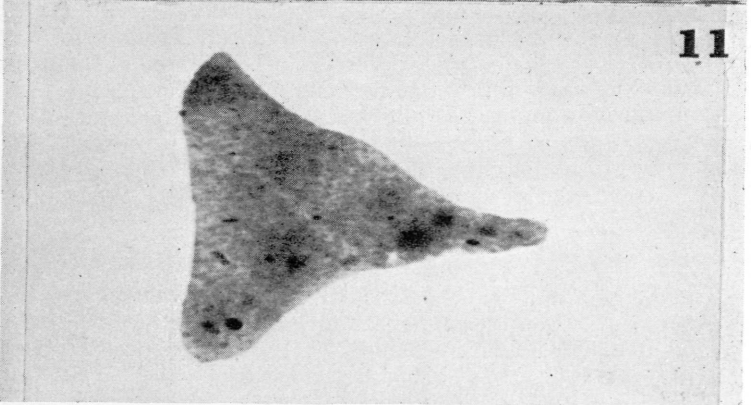
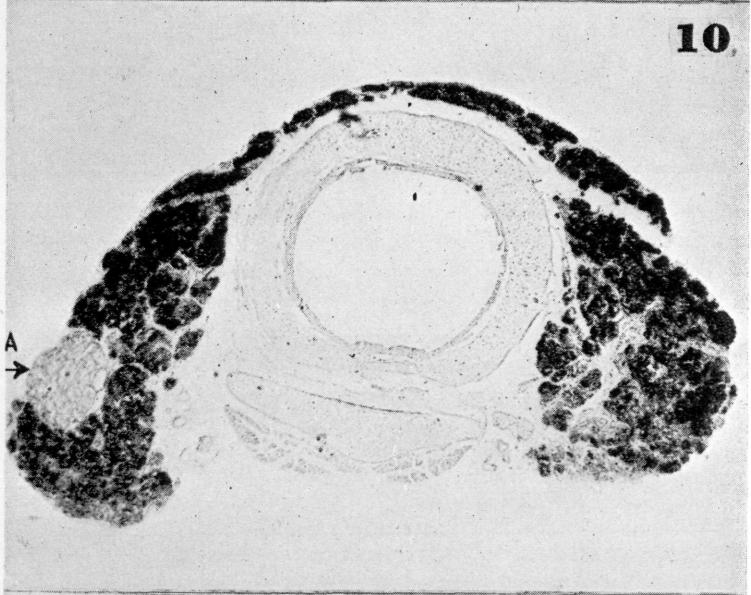
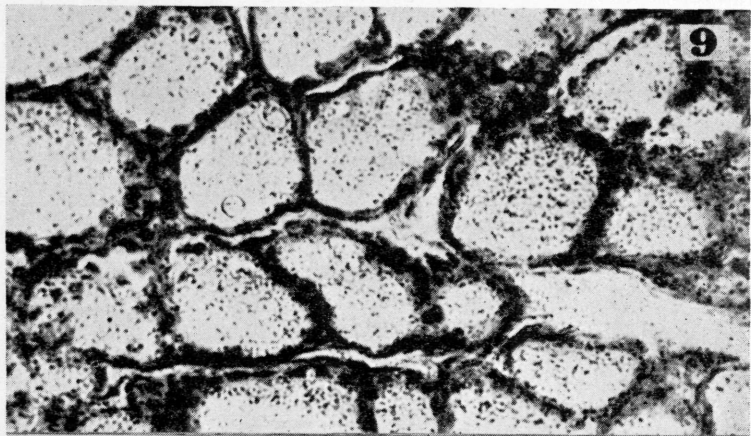
To demonstrate that the lactating rat breast serves as an excretory mechanism for excess iodine, as Rugh (1950) has shown for the lactating mouse, 100 $\mu$ c. radioiodine ( $I^{131}$ ) was added to the drinking water of a rat which had been nursing its litter. The nursing rats were removed and the mother was sacrificed the next day. The maternal mammary glands were removed and each disclosed a relatively high degree of radioactivity. Several of the glands were then thinned out by stretching and whole mount contact x-ray auto-radiographs were made (fig. 11). Due to the leaching out properties of unfixed iodides during the usual preparation of microscopic sections it was found advisable to use this gross section contact method with non-screen x-ray film.

*Part II.* Three pregnant rabbits each near term were used. The animals were anesthetized, the abdomen opened, and a single fetus of each of the three litters received one injection of radioactive iodine ( $I^{131}$ ) in the amount of 210, 500 and 500  $\mu$ c respectively. The radioiodine was mixed with a small amount of India ink just prior to injection. The abdominal wound was then closed and about twenty-four hours later the three pregnant rabbits were sacrificed. All the fetuses, including the three that were injected were found to be alive. The thyroid glands of the mothers and those of the fetuses were prepared in the usual manner for histological sections and for auto-radiography, employing the photosensitive emulsion coating method (Leblond, et al., 1948). Preliminary radioactivity assay with the Geiger counter disclosed considerable activity in all the thyroid gland material. The three fetuses which received the injected radioiodine were easily identified by the India ink discoloration and their thyroids were more radioactive than the others. All the auto-radiographs revealed the typical picture of radioiodine uptake with concentration in the colloid. (figs. 12-17)

---

#### EXPLANATION OF FIGURES, 9, 10, 11.

- FIGURE 9. Higher magnification of a portion of FIG. 8.  
FIGURE 10. Auto-radiograph. Cross-section of trachea and surrounding structures, nursing rat. Note the absence of radioiodine uptake in parathyroid gland, A.  
FIGURE 11. X-ray film auto-radiograph, gross section contact method. Lactating mammary gland of rat. Radioiodine administered in drinking water.





## RESULTS

*Part I.* All the auto-radiographs of the thyroids of both the pre-nursing and the nursing newborn rats showed considerable deposition of the black silver granules over the thyroid follicles. This reveals an appreciable uptake of the maternally administered radioiodine in the neonatal thyroid glands resulting from a transfer of the radioactive iodine across the placental barrier, in the one case, and across the breast parenchyma in the other.

Figures 1-4 are auto-radiographs of the thyroids of several prenursing rats. Figure 4 is of special interest since it is taken from a stillborn rat. This rat was one of two stillborn litter-mates, there having been a total of seven siblings in this litter. The autoradiograph of one of the five litter-mates born alive is shown in figure 3. Since the thyroids of both stillborns showed considerable uptake of  $I^{131}$ , the death of these animals must have occurred some time after the radioiodine was injected into the mother. It would appear then that the finding of radioactive iodine in the thyroid of a dead fetus following maternal injection of it, would indicate that fetal death had occurred sometime *after* the injection had been made. Conversely, had there been an absence of radioiodine in the thyroid of the stillborn, under these same conditions, it would have indicated that the animal had been dead *prior* to the injection of the mother. Thus, by the use of an innocuous tracer dose of radioiodine, maternally administered, one could determine whether fetal death occurred before or following some concurrent experimental procedure. Such a deduction, however, would be valid only after the fetal thyroid gland had become morphologically, functional, which in the rat is on the eighteenth or nineteenth day of fetal life, (Gorbman and Evans 1943).

Auto-radiographs of the thyroid glands of four of the nursing group of newborn rats are shown in figures 5-8. Those in figures 7 and 8 are from an older litter than are those in figures 5 and 6.

Figure 9 is a higher magnification of a portion of figure 8, and gives more of the detail of granule distribution.

Figure 10 is a cross section of the trachea and its surrounding structures in a nursing rat at the level of the thyroid isthmus. Note the lack of radioiodine uptake in the island of parathyroid tissue (A) which is almost free of black granules as contrasted with the intense distribution over the thyroid gland.

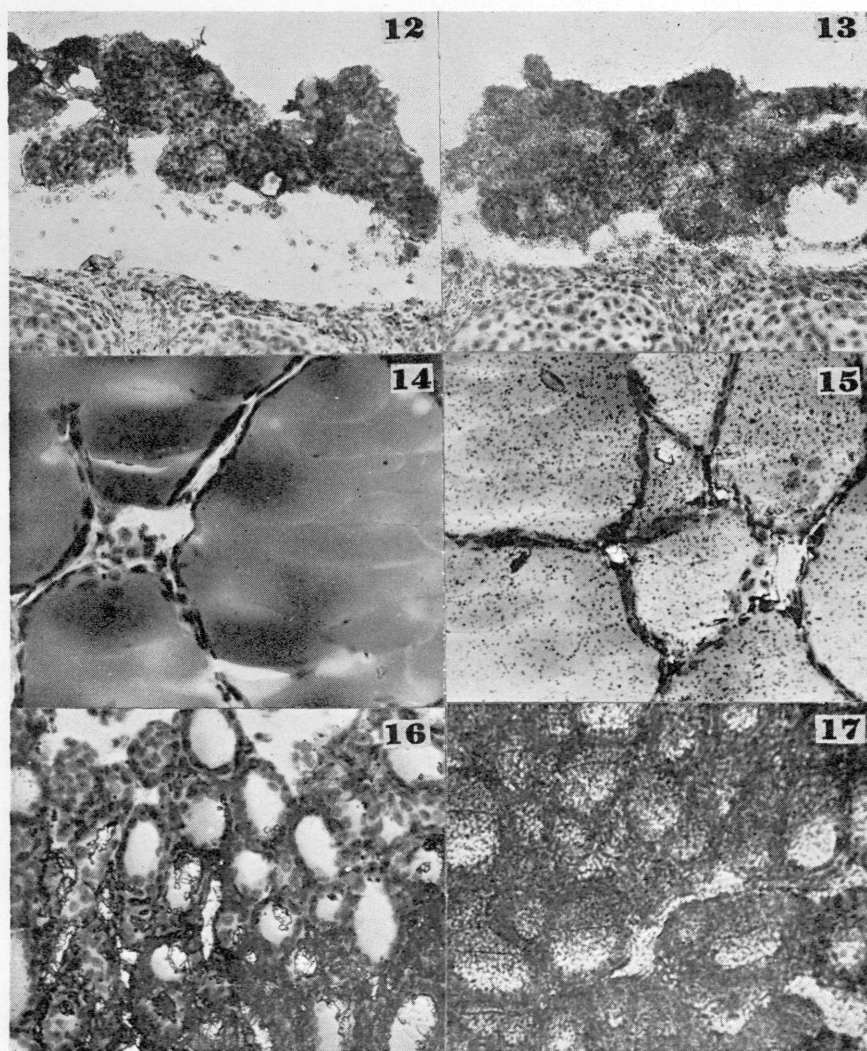
Figure 11 is a contact auto-radiograph of a lactating mammary gland of the rat that had received radioiodine in its drinking water.

*Part II.* All the auto-radiographs of both maternal and fetal thyroids indicated uptake of radioiodine. The accumulation of radioactive iodine in the thyroid glands of the pregnant rabbits following its injection into a fetus would indicate the transfer of that iodine across the placenta from *fetus* to *mother*. The fact that the sibling thyroids revealed considerable uptake of radioiodine indicates the transfer of radioiodine, first from the injected fetus across the placenta to the mother, and then back from the mother across the placenta to the other fetuses of the litter. There are no known vascular communications between litter mates, each fetus having its own discrete placenta. Thus the rabbit placenta in late gestation is pervious to iodine in either direction. Figures 12-17 show the histological sections and the corresponding auto-radiographs of the thyroid gland of one of the pregnant rabbits and of two of its fetuses. Histological sections are on the left, and the corresponding auto-radiograph on the right.

## DISCUSSION

There is no question but that the properties of the placenta with regard to the degree and selectivity of its permeability towards different substances vary with the stage of gestation. This fact was recognized by Krukenberg in 1885, and we ought constantly to bear in mind that the placenta is not a simple membrane, but to quote Gellhorn and Regnier (1936), "it represents a complex organ which itself produces

diverse chemical transformations." Thus it is only in a limited sense that the transfer of substances across the placenta follows the general laws that obtain for diffusion across permeable membranes. Among the determining factors are those of the crystalloid or colloid nature of the molecule or molecular aggregate, the molecular weight of the substance, the relative concentrations of the material on both sides of the placenta, and their hydrogen ion concentrations.



FIGURES 12-17. Histological section on left and corresponding autoradiograph on right.

FIGS. 12 and 13. Thyroid gland of fetus injected in utero with  $I^{131}$ .

FIGS. 14 and 15. Thyroid gland of mother of above injected fetus.

FIGS. 16 and 17. Thyroid gland of litter mate of above injected fetus.

The method of auto-radiography is a relatively simple and inexpensive technique for demonstrating the presence of very small quantities of radio-active materials in certain applicable situations. For the thyroid gland it reveals localization of

uptake. Where relative quantitative data will suffice instead of absolute quantitative values, auto-radiography can offer much to save time, labor, and special equipment. The laboriously precise analytical technique of Hudson (1931) could today be easily substituted by the much simpler one of auto-radiography, for to quote Hudson: "All I proposed to show by this experiment was whether or not inorganic iodides passed through the placenta and reached the thyroid of the fetus."

It should be emphasized that the passage of iodine across the placenta or breast is not synonymous with the transfer of circulating thyroid hormone across these structures. The placenta is most certainly impermeable to albumen-bound thyroid hormone (Schlossmann 1932). Moreover, Courrier and Aron (1929) and Dorff (1934) are of the opinion that the fetus obtains practically no thyroid hormone from the mother. This situation apparently also holds for thyrotropic hormone (Aron '30), insulin (Schlossmann 1931), pituitrin, adrenalin, parathyroid hormone (Snyder 1943) and prolactin B (Soule 1934). Carlson and Ginsberg (1941), however, have found that insulin is transferable across the placenta. That the nursing receives no thyroid hormone by way of the breast milk seems evident from the reports of Elmer and Rychlik (1934) and Dorff (1934). Rugh (1951) has found that the iodine present in the breast of the lactating mother mouse after injection of  $I^{131}$  is nearly all in the form of NaI. Apparently therefore, both the fetus and the infant must of necessity manufacture each its own thyroid hormone from the basic materials furnished by the mother, of which iodine is an essential component.

The increasingly widespread use of radioactive iodine as either a diagnostic or therapeutic agent impels one to add a word of extra caution if it is to be administered to a pregnant or lactating patient.

#### SUMMARY

1. Radioiodine  $I^{131}$  was injected into pregnant rats. The newborn were sacrificed *before* nursing. Auto-radiographs revealed a substantial collection of radioiodine in their thyroids, indicating the passage of iodine across the placenta from mother to fetus.
2. Radioiodine was injected into lactating rats. The newborn were sacrificed *after* nursing. Auto-radiographs showed a substantial uptake of radioiodine in their thyroids, indicating the passage of iodine across the breast.
3. Radioiodine was given by mouth to a lactating rat. Auto-radiographs showed a considerable accumulation of radioiodine in its mammary glands, indicating an excretory function of the lactating rat breast.
4. Radioiodine was injected into a single member of each litter of gestating rabbits. Auto-radiographs showed a substantial uptake of radioiodine in all the thyroid glands, including the maternal ones, indicating the passage of iodine across the placenta from the injected fetus to the mother, and then reversely across the placenta again from the mother to the siblings of the injected fetus.
5. Radioiodine may be of value from an investigative standpoint in determining whether fetal death occurred before or after a given experimental procedure.
6. Diagnostic or therapeutic use of radioactive iodine in the pregnant or lactating human subject merits careful consideration of its possible effect upon the young follicular cells of the developing thyroid gland of the fetus or new-born infant.

Grateful acknowledgment is given to Mrs. Ruth Sclar and Miss Virginia Schueller for their laboratory assistance.

#### LITERATURE CITED

- Aron, M. 1930. Sur l'Imperméabilité du Placenta à la Substance Préhypophysaire Active sur la Glande Thyroïde. *Compt. Rend. Soc. de Biol.*, 103: 151-152.



- Bélanger, L. F., and C. P. Leblond.** 1946. Method for Indicating Radioactive Elements in Tissues by covering Histological Sections with Photographic Emulsion. *Endocrin.*, 39: 8-13.
- Carlson, A. J., and H. Ginsberg.** 1914. The Influence of Pregnancy on the Hyperglycemia of Pancreatic Diabetes. *Am. J. of Physiol.*, 36: 217-222.
- Courrier, R., and Aron, M.** 1929. Sur le Passage de l'Hormone Thyroïdienne de la Mère au Foetus. *Compt. Rend. Soc. de Biol.*, 100: 839-841.
- Curtis, Geo. M., and M. B. Fertman.** 1943. Iodine in Nutrition. *J.A.M.A.*, 121, No. 6: 423-430.
- DeLée, J. B., and J. P. Greenhill.** 1947. *Obstetrics* Ed. 9. W. B. Saunders Co., Phila., p. 292.
- Dorff, G. B.** 1934. Sporadic Cretinism in One of Twins. *Am. J. Dis. Child.*, 48: 1316-1325.
- Elmer, A. W., and W. L. Rychlik.** 1934. L'Elimination de l'Iode par la Colostrum et par le Lait pendant l'Accouchement chez la Femme, *Compt. rend Soc. de Biol.*, 117: 530-532.
- Gelhorn, A.** 1943. Placental Transmission of Radioactive Isotopes. *Proc. of the Conf. on Problems of Human Fertility*, pp. 158-166. Geo. Banta Publishing Co., Menasha, Wis.
- Gelhorn, E., and J. Regnier.** 1936. La Perméabilité. Masson et Cie. Libraires de l'Academie de Médecine, Paris, pp. 714-722.
- Gorbman, A., and H. M. Evans.** 1943. Beginning of Function in the Thyroid of the Fetal Rat. *Endocrin.*, 32: 113-115.
- Gusserow, A.** 1872. Zur Lehrer vom Stoffwechsel des Foetus. *Arch. f. Gynak.*, 3: 241-270.
- Hamilton, J. G.** 1942. The Use of Radioactive Tracers in Biology and Medicine. *Radiology*, 39: 541-572.
- Hertz, S., A. Roberts and R. D. Evans.** 1938. Radioactive Iodine as an Indicator in the Study of Thyroid Physiology. *Proc. Soc. Exp. Biol. and Med.*, 38: 510-513.
- Hudson, G. E.** 1931. The permeability of the Placenta to Inorganic Iodides. *J.A.M.A.*, 97: 1513-1517.
- Krukenberg, G.** 1885. Zur Frage der fötalen Nierensecretion und der Fruchtwasserbildung. *Arch. f. Gynak.*, 26: 258-272.
- Leblond, C. P., W. L. Pervical, and J. Gross.** 1948. Autographic Localization of Radioiodine in Stained Sections of Thyroid Gland by Coating with Photographic Emulsion. *Proc. Soc. Exp. Biol. and Med.*, 67: 74-76.
- Lundahl, Walter S., J. Meites, and L. F. Wolternik.** 1950. A Technique for whole Mount Autoradiographs of Rabbit Mammary Glands. *Science*, 112: 599-600.
- Mayer, Professor.** 1817. Versuche welche den Uebergang tropfbarrer Flüssigkeiten von der Mutter an und in den Fötus erweisen Med. *Chirurgische Zeitung*, 2: 431-432.
- Mossman, H. W.** 1925. The Rabbit Placenta and the Problem of Placental Transmission. *Am. J. of Anatomy*, 37: 433-497.
- Nicoloux, M.** 1909. Passage des Substances Chimiques de la Mère au Foetus, *L'Obstetrique*, Deuxième année, nouvelle serie, Paris, pp. 840-865.
- Reijst-Scheffer, A.** 1908. De overgang van iodidem in melk, *Pharm. Weekbl. voor Nederland*, 45: 1359-1362.
- Rugh, R.** 1950. Radioactive Iodine and the Nursing Mouse. *Anat. Rec.*, Vol. 106, No. 2: 242.
1951. The Mouse Thyroid and Radioactive Iodine. *Jour. Morph.*, 89(2): 323-362.
1951. Radioiodine and Histopathological Effects. *Jour. Morphol.* 89(3): 457-497.
- Scharrer, K.** 1927. Die Jodanreicherung der Milch durch Jodfütterung, *Ztschr. f. d. ges. exper. Med.*, 56: 677-697.
- Schauenstein, A., and S. Schauenstein.** 1859. Ueber dem Uebergang medicamentöser Stoffe aus dem Kreislaufe der Säugenden in ihre Milch und aus dem Kreislaufe der Swangeren in ihr Fruchtwasser und irhen Fötus, *Jahrbuche der Kinderheilkunde und physischen Ergiehung*, 2: 13-18.
- Schlossman, H.** 1931. Ist die Plazenta für Insulin durchlässig? *Arch. für Exper. Pathol. und Pharm.*, 159: 213-222.
1932. Der Stoffaustansch zwischen mutter und Frucht dursh die Placenta, *Ergenbisse der Physiol.*, 34: 741-811.
- Smith, G. E.** 1917. Fetal Athyreosis. *J. Biol. Chem.*, 29: 215-225.
- Snyder, F. F.** 1943. Placental Transmission in Relation to the Stage of Pregnancy. *Proc. of the Conf. on Problems of Human Fertility*, pp. 144-157. Geo. Banta Publishing Co., Menasha, Wis.
- Soule, S. D.** 1934. The Impermeability of the Placenta to Prolan B. *Am. J. Obstet.*, 27: 723.